REMARKS

Upon entry of this response, claims 1-28 will be pending.

The Invention of Claims 1-20 Are Not Different From That of Claims 21-28

The Office Action alleges that claims 21-28 are "directed to a non-elected invention" as they are directed to a method of "preventing", as opposed to the previously examined method for "treating" of claims 1-20. Accordingly, the Office withdrew claims 21-28. Specifically, the Office Action alleges that the

> examined claims and the newly submitted claims are directed to two distinct methods that use **different reagents** and have **different goals**.

The Office Action, page 2, emphasis added. Contrary to the Office Action's allegation, the examined claims 1-20 and claims 21-28 use the same "reagents" and have the same "goal". The claims' common "reagent" is botulinum toxin, and common "goal" is to alleviate the headache pain of a medication overuse disorder.

Thus, the inventions of claims 1-20 and that of 21-28 are not different, and should not be subjected to a restriction requirement. Applicant respectfully requests the Office to reinstate claims 21-28 and examine same.

The Claims Are Not Obvious

Claims 1-20 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Katsarava et al. in view of Aoki et al. Specifically, the Office Action's allegation is based on the following erroneous logic:

(i) Botulinum toxin can treat tension headache (TH) (Aoki et al.);

(ii) TH is associated with medication overuse disorder (MOD) (Katsarava et al.);

(iii) Therefore, it is obvious to use botulinum toxin to treat MOD because botulinum toxin can treat TH.

The above logic is flawed because the use of a medication to treat TH does not necessarily treat MOD. In fact, it has been shown that the use of a medication (e.g. triptan) to treat TH can **cause** MOD (Katsarava et al., page 1682, first column, discloses that MOD develops after use of headache medications such as triptan).

Further, following through with the logic of the Office Action, **Katsarava et al. would actually teach away** from the claimed invention because Katsarava et al. teaches that MOD can be treated by **withdrawing** (stop administering) a medication, whereas the claimed invention recites an **administration** of a medication (i.e., botulinum toxin) to treat MOD.

Thus, the Office Action's logic is flawed, and the claimed invention is not obvious.

Request For the Office to Address Applicant's Scientific and Legal Arguments Previously Presented

Based on detailed scientific evidence/reasoning and authoritative case law, Applicant has previously presented a number of arguments for why the Office Action's logic is flawed, and why the claimed invention is not obvious. The Office has not addressed any of Applicant's arguments. Applicant hereby resubmits these arguments below and respectfully requests the Office to address same. (The Office Action page numbers referenced below are with respect to the Office Action mailed May 12, 2005).

A. Scientifically Nonobvious

Katsarava et al. teach that patients with migraine headaches, tension-type headaches, and a combination of migraine and tension-type headaches can suffer from medication overuse headaches. However, patients suffering from tension-type headaches are more likely to relapse from withdrawal of medication than patients suffering from migraines particularly when the medicament is an analgesic. Aoki et al. teach a method for treating a tension headache by administration of botulinum toxin.

Page 3 of the Office Action argues that it would be prima facie obvious to use botulinum toxin to treat patients that have medication overuse disorder because: 1) Katsarava et al teach that medication overuse disorder is associated with patients that have tension-type headaches, 2) those with tension-type headaches are more likely to get medication overuse headaches and 3) Aoki et al teach that botulinum toxin can be used to treat patients that suffer from tension-type headaches. However, this reasoning is logical only if tension-type headaches directly cause medication overuse headaches or medication overuse headache manifest via the same mechanism as tension-type headaches. Mere association of two different pains and likelihood of occurrences are insufficient to warrant obviousness by the combined references.

1. Tension-type headaches do not directly cause medication overuse headaches.

To draw a causal relationship between tension-type headaches and medication overuse headaches, tension-type headaches must be necessary and sufficient to cause medication overuse headaches. However, tension-type headaches are not necessary to cause medication overuse headache because in the absence of tension-type headache, medication overuse headaches can still occur. For example, Table 1 of Katsarava et al. shows that 22% of the patients with migraine headaches and not tension type-headaches relapsed upon withdrawal of medication. Also, tension-type headaches are not sufficient to cause medication overuse headaches because the presence of tension-type headache alone will not cause medication overuse headache without the overuse of the medication.

In addition, in the very first paragraph of Katsarava et al. it is pointed out that "the International Headache Society (IHS) defines medication overuse headache (MOH) as a chronic headache (on>15 days/month) that develops after overuse of acute headache *medication*...and vanishes after withdrawal." Likewise, in the Eross (2003) article provided by the examiner, on page E9, column 2 the author states, "[a]ny *medication* that is taken to treat an individual headache attack is thought to be able to cause MOH." (Emphasis added by Applicant).

Viewed from a different perspective, medication overuse headaches are merely side effects of the medication used to treat tension-type headaches. Thus, the tension-type headaches do not cause the side effect but rather coexist because of the medication. There are two ways to treat a side effect. Stop taking the drug (and take a different drug if necessary) or take a medication to treat the side effect. Here, the therapy of choice is to stop taking the drug because there are currently no therapeutic agents to combat the side effects. This invention provides an alternative treatment for the medication overuse side effect.

Thus, since tension-type headaches are neither necessary nor sufficient for medication overuse headaches, tension-type headaches are not the cause of medication overuse headaches but rather the medication itself as defined by experts. If tension-type headaches do not cause medication overuse headaches then the treatment for tension-type headaches will not necessarily be effective to treat medication overuse headaches.

2. Tension-type headaches and medication overuse headaches do not manifest via the same mechanism.

The mechanism causing tension-type headaches is different from the mechanism causing medication overuse headaches. Tension-type headaches are caused by muscle contraction. Botulinum toxins are known to relax muscles. Thus, as in Aoki et al., tension-type headaches can be treated by relaxing the muscles via administration of botulinum toxin. Medication overuse headache does not appear to be caused by muscle contraction but rather due to neuroplasticity, i.e. changes in neurochemistry and receptor expression (see Tepper and Dodick, Debate: Analgesic overuse is a cause, not a consequence, of chronic daily headache, *Headache*, 2002; 42:543-554). Therefore, it is not obvious from Aoki et al. to treat a headache that is not caused by muscle contractions with a botulinum toxin.

3. Inaccuracies in the Office Action

If the reasoning in the Office Action is correct (i.e. a drug that is effective in treating tension type headaches should also be effective in treating medication overuse headaches because those who are likely to get tension-type headaches get medication overuse headaches) then the same drugs that are used to treat tension-type headaches (analgesics, triptans and narcotics) should also be effective in treating medication overuse headaches. But this is not true since the drugs used to treat tension-type headaches are the cause of medication overuse headaches. For this reason the treatment of choice is to

discontinue the use of the medication to treat tension-type headache and detoxify the patient.

Furthermore, page 5 of the Office Action argues that if tension-type headaches are treated with botulinum toxin then the patient would suffer less headaches, there would be less frequent occurrences of medication overuse relapse, therefore it is obvious to treat medication overuse headache with botulinum toxin. However, as applied to the current invention this reasoning is flawed by the presumption that tension-type headaches are treated with botulinum toxin. This invention applies to those who are suffering from medication overuse headache not tension-type headache. This means that the patient has already undergone treatment of a tension-type headache with traditional therapeutic agents and is now suffering from medication overuse headache. As such the claims are directed to pain associated with a medication overuse disorder and not tension headaches and it is clear that tension headaches are not the same as medication overuse headaches nor is a medication overuse headache directly caused by tension-type headaches. If two types of pain are mechanistically different and have different etiologies, then it is not obvious that they can be treated with the same therapeutic agents.

B. Nonobviousness

It appears that the Office Action is merely suggesting that since medication overuse headache occurs most commonly in those with tension-type headaches and botulinum toxin has been suggested as a treatment for tension-type headaches, it would be "obvious to try" botulinum toxin for medication overuse headaches. However, "obvious to try" is not the proper standard for obviousness. In *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir., 1988), the court stated, "It is true that this court and its predecessors have repeatedly emphasized that 'obvious to try' is not the standard under § 103." The court then laid out two kinds of errors that lead to an "obvious to try" analysis, one of which is relevant here. The court stated, "what would have been 'obvious to try' would

have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of may possible choices is likely to be successful." In *In re O'Farrell*, the prior art laid out all the parameters encompassed by the claims, therefore, it was not obvious to try what the claims taught and obviousness-type rejection was warranted. Here too, Aoki et al. lays out parameters in claims 1, 2, 13 and Example 12, specifically, headaches or tension headaches associated with muscle contractions. Thus, headaches within the parameter of being associated with muscle contractions would warrant rejection under § 103, but headaches not associated with muscle contractions would merely be "obvious to try." However, since medication overuse headaches are not tension-type headaches and are not thought to be associated with muscle contraction (but rather neuroplasticity), the claims of this invention fall outside the parameters of Aoki et al. Therefore, obviousness-type rejection is not warranted.

Finally, in *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1330 (Fed. Cir., 2003), the patent claims were directed to methods of "treating or preventing macrocytic-megaloblastic anemia" by administering a combination of folic acid and vitamin B12 "to a human in need thereof." Rexall marketed over-the-counter dietary supplement that contained folic acid and vitamin B12 in the claimed range, however, the dietary supplement was labeled and advertised for maintenance of proper blood homocysteine levels, and not for prevention or treatment of macrocytic-megaloblastic anemia. *Id.* at 1331. The court found that the dietary supplement did not infringe the patent because claim language, "to a human in need therof" breathed life and meaning to the preamble "treating or preventing macrocytic-megaloblastic anemia." *Id.* at 1333. Therefore, to infringe this patent the accused device must be used for the purpose stated in the preamble. Similarly, in Aoki et al. the preamble in the independent claims are directed to headaches or tension headaches and conclude by stating that the invention relieves

headaches associated with tension headaches or muscle contractions. Thus, for an invention to read on these claims it must treat a headache or tension headache associated with muscle contractions.

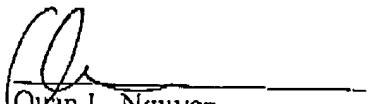
The claims in the present application are not directed to tension headaches or headaches associated with muscle contraction but rather medication overuse disorder. Therefore, the claims are patentable over Katsarava et al. in view of Aoki and withdrawal of the rejection is requested.

Provisional Double Patenting Rejection

Applicant acknowledges the Office Action's comments regarding the provisional double patenting rejection with respect to co-pending Application No. 11/039,506. Since this is a provisional rejection, Applicant will address the rejection upon an indication of allowable claims.

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,



Quan L. Nguyen
Registration No. 46,957

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COZEN O'CONNOR
1900 Market St.
Philadelphia, PA 19103
(215) 665-2158 (Telephone)
(215) 701-2057 (Facsimile)

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